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EXAMINER	
DAVIS, MINH TAM B	
ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/763,393	PASTAN ET AL.	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03/15/06;03/20/06*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6-12,14-18 and 53-60* is/are pending in the application.

4a) Of the above claim(s) *9-12,16,19-52 and 58-60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-8,14,15,17,18 and 53-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/15/06*.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. *03/10/06*.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicant cancels claims 3, 5.

Accordingly, claims 1-2, 4, 6-8, 14-15, 17-18, 53-57 are examined in the instant application.

The following are the remaining rejections.

Election/Restrictions

Applicant argues that the claimed polypeptide and polynucleotide share a special technical feature. Applicant argues that all the claimed proteins share a special technical feature, namely that they include 8 to 10 contiguous amino acids of SEQ ID NO:1.

Applicant's arguments in papers of 03/15/06 and 03/20/06 have been considered but are not found to be persuasive for the following reasons:

The claimed polypeptide and polynucleotide do not share a special technical feature, because they do not share a common structure.

Similarly, although the claimed different proteins share some 8 to 10 common contiguous amino acids with SEQ ID NO:1, they do not share common full length structure, which structure encompasses more than just some fragments thereof, and which full length structure confers critical properties and characteristics of the full length proteins, that are not shared by the common fragments.

The requirement is still deemed proper and is therefore made FINAL.

Drawings

The submitted amended drawing of figures 4 and 5 is acknowledged and entered.

Claim Rejections - 35 USC § 112, Written Description

Claims 1-2, 4, 6-8, 15, 17-18, 54-57 remain rejected under 112, first paragraph, written description for lack of a clear written description of 8 to 10 contiguous amino acids of SEQ ID NO:1, which bind MHC I, for reasons already of record in paper of 09/13/05.

A. **(i)** Applicant argues that the claims are directed to 8 to 10 consecutive amino acids of SEQ ID NO:1, and are not broadly directed to molecules from other species. Applicant argues that in addition, the claims are limited to polypeptides having a specified function, namely that they bind MHC and can be used in induce immune response.

Applicant's arguments in papers of 03/15/06 and 03/20/06 have been considered but are not found to be persuasive for the following reasons:

Due to the open language "a polypeptide comprising 8 to 11 contiguous amino acids of SEQ ID NO:1" of claim 1, the polypeptides of claims 1, 2, 7, 17 encompass unknown sequences attached to 8 to 11 contiguous amino acids of SEQ ID NO:1. The specification however does not disclose the structure of these numerous sequences attached to to 8 to 11 contiguous amino acids of SEQ ID NO:1.

Further, the claims are drawn to a genus of peptide fragments of SEQ ID NO:1 that bind to MHC class I, wherein the peptide fragments do not share a common structure, because different regions of SEQ ID NO:1 are structurally different.

Moreover, binding to MHC class I per se is not a critical function of the claimed peptides, which function distinguishes the claimed invention from other, because there exist numerous peptides, which do not share the same structure with SEQ ID NO:1 or fragments thereof, but which also bind to MHC class I molecules (see disclosure in the instant specification on page 20, last paragraph), and because binding to MHC I does not necessarily correlate with the ability to induce CTL response and lysis of primary cancer cells by said CTLs, in view that not any peptides that bind to MHC could induce CTL response and lysis of primary cancer cells by said CTLs. For example, Visseren et al, 1997, Intl J Cancer, 73(1): 125-30, teach that some peptides of MAGE-2, although fitted into the binding motif for binding to HLA-A0201, do not bind to the HLA molecule with sufficient affinity (p.127, first column, first paragraph, table I on page 127). Further, Visseren et al teach even some peptides that bind to the HLA molecule with high affinity at 4^0 C, they do not bind with high affinity at 37^0 C, and therefore are less likely to form stable complexes in vivo and have a lower chance to appear in HLA-A0201 molecule at the cell surface (p.127, first column, second paragraph).

Thus, **since binding to MHC class I per se is not a critical function of the claimed peptides, and since there is no common structure for the claimed peptides, there is no correlation between function and the claimed peptides.**

(ii) Applicant argues that functional domains of SEQ ID NO:1 are disclosed, which describes similarity of SEQ ID NO:1 with GAGE and MAGE proteins, and the RGD motifs, involved in protein-protein interaction.

Applicant's arguments in papers of 03/15/06 and 03/20/06 have been considered but are not found to be persuasive for the following reasons:

Although the specification discloses sequence alignment of SEQ ID NO:1 with GAGE and MAGE proteins, there is no disclosure of which 8-11 peptides of SEQ ID NO:1 that are similar to those 8-11 peptides of GAGE or MAGE proteins, wherein said peptides bind to MHC class I, and could induce CTLs response and lysis of primary cancer cells by said CTLs, a critical function of the claimed peptides. In addition, although the specification discloses the motif RGD involved in protein-protein interaction, the claims are not drawn to the motif RGD involved in protein-protein interaction.

Thus, it is clear that **the structure of which 8-11 amino acids peptides of SEQ ID NO:1, that bind to MHC, and could induce CTLs response and lysis of primary cancer cells by said CTLs, is not disclosed in the specification.**

In view of a lack of a correlation between structure and function of the claimed 8-11 amino acids peptides, and a lack of representative species, the specification and the claims do not meet the standards as shown in the examples of Lilly or Enzo.

In summary, the specification and the claims do not meet 112, first paragraph, written description requirement. One of skill in the art would conclude that Applicant did not have possession of the claimed genus of peptides, at the time the invention was made.

B. **(i)** Applicant argues that the specification discloses that epitopes of use are 8-10 amino acids in length and have anchoring residues, such as at positions 2 and 9. Applicant argues that the claimed PAGE4 polypeptides can be 9 or 10 amino acids in length, and can include binding motifs for HLA-A2. Applicant argues that the claimed peptides have specific anchoring residues in second position (A, L, I, V, M or S) and a positively charged amino acid at position nine.

Applicant's arguments in papers of 03/15/06 and 03/20/06 have been considered but are not found to be persuasive for the following reasons:

Since binding to MHC class I per se is not a critical function of the claimed peptides, there is no correlation between function and the claimed peptides of 8 to 11 amino acids of SEQ ID NO:1, supra.

Further, the disclosed peptides of 9 or 10 amino acids in length, with **anchoring amino acids at position 2 and 9** that bind to MHC class I, are drawn to a genus of peptides that bind to MHC class I, **with any binding affinity**, and **is not a sufficient description for the encompassed subgenus of the MHC class I binding-peptide fragments of SEQ ID NO:1,** because the genus of 9 or 10 amino acid peptides disclosed in the art do not share the same amino acids at positions 1, 3-8, or 10 as the MHC class I binding-peptide fragments of SEQ ID NO:1, and because amino acids 1, 3-8, or 10 of an 8-10 amino acids peptide also significantly influence its binding affinity to MHC class I, wherein a sufficient affinity binding is critical for inducing CTL response and lysis of primary cancer cells by said CTLs. For example, Grey et al (WO 94/020127 A1, 09/15/04) teaches that positions other than the anchor positions 2 and 9 have a role in MHC A2.1 binding, and that most of the deleterious effects on binding are induced by charged amino acids in non-anchor position (p.49, last paragraph). Grey et al further teaches that for A2.1 motif for 9-mer peptides, the acidic amino acids and the amino acid P at position 1, the acidic and basic amino acids at position 3, the basic amino acids at position 6, and the acid and basic amino acids at position 7 would have negative effect for the peptide binding to HLA-A2.1 (p.49 and table 9 on page 50). Further, Visseren et al, 1997, Intl J Cancer, 73(1): 125-30, teach that even some peptides of MAGE-2, that fit into the binding motif for binding to HLA-

A0201, do not bind to the HLA molecule with sufficient affinity (p.127, first column, first paragraph, table I on page 127). Further, Visseren et al teach even some peptides that bind to the HLA molecule with high affinity at 4^0 C, they do not bind with high affinity at 37^0 C, and therefore are less likely to form stable complexes in vivo and have a lower chance to appear in HLA-A0201 molecule at the cell surface (p.127, first column, second paragraph). Thus, in view of the teaching in the art, without the description of which 8-11 peptides of SEQ ID NO:1 actually bind MHC class I with such affinity that it could induce CTL response and lysis of primary cancer cells by said CTLs, one cannot predict which peptide fragment of SEQ ID NO:1 has the critical function of binding MHC class I with such affinity that it could induce CTL response and lysis of primary cancer cells by said CTLs.

In summary, since the described genus of peptides with anchoring amino acids at positions 2 and 9 do not share a common structure and critical function with the encompassed subgenus of peptide fragments of SEQ ID NO:1, there is no correlation between structure of the claimed peptide and its critical function. In view of a lack of a correlation between structure and function of the claimed 8-11 amino acids peptides, and a lack of representative species, the specification and the claims do not meet the standards as shown in the examples of Lilly or Enzo.

(ii) Applicant argues that method for selection for binding motifs that bind HLA-A2 is disclosed, and in addition, methods for testing the immunogenecitiy of a specific epitope are provided and also known in the art. Applicant submits a Declaration by Dr. Pastan, asserting that using the method provided by the specification, immunogenic PAGE4 polypeptides are generated, and are found to activate cytotoxic T cells (CTLs), wherein the CTLs are able to lyse prostate cancer cells expressing PAGE4.

The submission of the Declaration by Dr. Pastan is acknowledged and entered.

Applicant's arguments in papers of 03/15/06 and 03/20/06 have been considered but are not found to be persuasive for the following reasons:

Although the method for screening peptides that bind to MHC class I is well known, however, the 112, first paragraph, written description requires that Applicant had possession of the claimed invention at the time the invention was made. Since, the finding in the Declaration by Dr. Pastan **is post-filing,** the data from the Declaration could not be used for obviating the 112, first paragraph, written description.

Moreover, a single P16 peptide disclosed in the Declaration is not a representative species. The claims encompass a genus of peptide fragments of SEQ ID NO:1 that bind to MHC class I, wherein the peptide fragments do not share a common structure, because different regions of SEQ ID NO:1 are structurally different.

In view of a lack of a correlation between structure and function of the claimed 8-11 amino acids peptides, and a lack of representative species, the specification and the claims do not meet the standards as shown in the examples of Lilly or Enzo. Thus, the specification and the claims do not meet 112, first paragraph, written description requirement. One of skill in the art would conclude that Applicant did not have possession of the claimed peptides at the time the invention was made.

Claim Rejections - 35 USC § 101, Utility

Claims 1-2, 4, 6-8, 14-15, 17-18, 53-57 remain rejected under 35 USC 101, for lack of a specific and substantial utility, for reasons already of record in paper of 09/13/05.

The level of the polypeptide SEQ ID NO:1 in primary cancer cells

Applicant argues that only one of the cited references describes a comparison of mRNA and protein in tumor cells, and that none of the references describe results obtained in carcinomas. Applicant argues that Ornoft et al, 2002, teach that although it was only possible to compare mRNA and protein in a few carcinoma cases, there was a good correlation between transcript alterations and protein levels. Applicant submits a Declaration by Dr. Pastan, and a post-filing reference by Iavrone et al, 2002, asserting that the claimed polypeptide SEQ ID NO:2 was discovered before the filing date of the instant application, and that using the polyclonal antibodies described in the specification, the presence of the PAGE4 polypeptide in five patients with prostate cancer expressing PAGE-4 mRNA is confirmed.

The submission of the Declarations by Dr. Pastan, and the recitation of Ornoft et al, 2002, Iavrone et al, 2002, is acknowledged and entered.

Applicant's arguments in papers of 03/15/06 and 03/20/06 have been considered but are not found to be persuasive for the following reasons:

It is noted that the claimed polypeptide is SEQ ID NO:1 and not SEQ ID NO:2. It is further noted that, although the claimed polypeptide is discovered before the filing date of the instant application, the presence of the PAGE4 polypeptide in five patients with prostate cancer expressing PAGE-4 mRNA disclosed in the Declaration by Dr. Pastan, and the Iavrone et al, 2002, references are obtained **post-filing**, thus confirming that at the time the invention was made, further experimentation was required to determine whether SEQ ID NO:1 or fragments thereof that bind to MHC class I are of any use. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-

testing." *Brenner*, 148 USPO at 696. The disclosure does not present a substantial utility that would support the requirement of 35 U.S.C. 101.

It is further noted that no data is found from the Declaration concerning the expression of PAGE-4 mRNA and protein in five prostate cancer patients. Further, the statement from the Declaration concerning expression of PAGE-4 mRNA in prostate cancer patients seems to be contradictory to the disclosure in the instant specification. For example, in figure 4 of the instant application, the level of mRNA encoding SEQ ID NO:1 is almost undetectable, as compared to an abundant amount of said mRNA in normal prostate.

Moreover, in the submitted reference by Iavrone et al, 2002, it is not clear whether PAGE-4 protein and mRNA are the same as the claimed SEQ ID NO:1 and the encoding mRNA thereof. Further, since figures 1 and 3 in the submitted Iavrone et al reference are not readable, it is not clear whether PAGE-4 mRNA and protein are over- or under-expressed in prostate cancer, as compared to normal prostate.

Thus, further experimentation is required to determine whether SEQ ID NO:1 or fragments thereof that bind to MHC class I are of any use.

In addition, the cited references Brennan et al, Zimmer et al, Eriksson et al, Hell et al, and Guo et al, all of record, clearly show that the unpredictability of protein level, when based solely on the level of the encoding nucleic acid, applies to a variety of proteins, as well as different cancers, including carcinomas. For example, Hell et al, of record, teach that cells in all types of Hodgkin's disease exhibited high levels of bcl-2 mRNA, while the expression of the Bcl-2 protein was not homogenous to said cells. Similarly, Fu et al (EMBO Journal, 1996, Vol. 15, pp. 4392-4401) teach that levels of p53 protein expression do not correlate with levels of p53 mRNA

levels in blast cells taken from cancer patients with acute myelogenous leukemia, said patients being without mutations in the p53 gene. This is also confirmed in carcinoma, as shown in the teaching of Yokota, J et al (Oncogene, 1988,Vol.3, pp. 471-475), who teach that the retinoblasma (RB) 115 kD protein is not detected in all nine cases of lung small-cell carcinoma, with either normal or abnormal size mRNA, whereas the RB protein is detected in three of four adenocarcinomas and all three squamous cell carcinomas and one of two large cell carcinomas expressing normal size RB mRNA. Further, although Orntoft et al teach that the level of 19 proteins is correlated with that of the encoding mRNA, Orntoft et al also teach that other 7 proteins, from the total of 26 proteins, do not show a correlation between the protein level and that of the encoding mRNA. Thus, clearly in view of the teaching in the art, **which protein does have a correlation with that of the encoding mRNA cannot be predicted**. Based on the teaching in the art, one would conclude that the levels of polynucleotide mRNA transcripts cannot be relied upon to anticipate levels of protein expression.

In summary, because of such unpredictability, at the time the invention was made, one cannot determine whether SEQ ID NO:1 is overexpressed in "primary" cancer cells, such that they could be recognized and lysed by CTLs specific for SEQ ID NO:1. Further experimentation is required to determine what use is for the claimed polypeptide SEQ ID NO:1 or its fragments at the time the invention was made. Thus the claimed SEQ ID NO:1 and its 8-11 contiguous amino acids fragments that bind to MHC class I lack specific and substantial utility.

The unpredictability of cancer treatment

(1) Applicant argues that Smith et al teach that there are new studies, such as with MAGE-1 in melanomas, that can potentially be used to augment T cell responses, and thus

acknowledging that the use of tumor antigens, or fragments of a tumor antigens, can potentially be of use in treatment.

The arguments are not found to be persuasive. Smith et al teach that antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells (p. 847, last paragraph bridging p.848 and p.848). Smith further teaches that many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limits the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specfic antigen in the necessary MHC context (p.484). Further, although some cancer antigens could be used for treating cancer, **which cancer antigen could be used for treating cancer is not predictable**, in view of the overwhelming indication from the teaching in the art that cancer treatment is unpredictable.

Thus, although some cancer antigen could be used for treating cancer, however in view of the overwhelming indication from the teaching in the art that cancer treatment is unpredictable, one cannot determine whether the claimed SEQ ID NO:1, or its fragments could be used for treating cancer. Further experimentation is required to determine what use is for the claimed polypeptide SEQ ID NO:1 or its fragments at the time the invention was made. Because of this, the specification and the claims lack specific and substantial utility.

(2) Applicant argues that Boon et al state that for several tumor antigens, it is possible to obtain from syngeneic animals highly specific cytotoxic T lymphocytes, and that once tumor antigens are identified, they can be used for active immunization to elicit antitumoral response in

cancer patients. Applicant acknowledges that Boon teach that there are problems with tolerance, but argues that there may be problems with an approach does not negate the approach.

The arguments are not found to be persuasive. In addition to the problem that large tumor burdens can tolerize or at least depress the capability to respond against the tumor (Boon et al, p. 206, para 2), Boon et al also teach **even if activated CTLs are significantly increased, the therapeutic success remains unpredictable** due to inconsistencies in antigen expression or presentation by tumor cells (p.178, paragraph before last paragraph).

Thus, although the approach for treating using CTLs is not dismissed, and although highly specific cytotoxic T lymphocytes could be generated by some proteins, however, in view of the teaching of the art, which proteins could be successfully used for producing CTLs that are effective in treating cancer cannot be predicted.

In summary, in view of the overwhelming indication from the teaching in the art that cancer treatment is unpredictable, one cannot determine whether the claimed SEQ ID NO:1 could be used for treating cancer. Further experimentation is required to determine what use is for the claimed polypeptide SEQ ID NO:1. Because of this, the specification and the claims lack specific and substantial utility.

(3) Applicant argues that although Ezzel and Spitler suggest that cancer vaccines will not work, that does not mean that the claimed polypeptide and methods have no utility.

The arguments are not found to be persuasive.

In view of the overwhelming indication from the teaching in the art that cancer treatment is unpredictable, and in view of a lack of a correlation between SEQ ID NO:1 and cancer treatment, one cannot determine whether the claimed SEQ ID NO:1 could be used for treating

cancer. Further experimentation is required to determine what use is for the claimed polypeptide SEQ ID NO:1. Because of this, the specification and the claims lack specific and substantial utility.

(4) Applicant further argues that the Patent and Trademark office, such as US 6,756,038, US 7,005,498, US 6,419,931, seems to agree that antigenic peptides can be used for induce specific immune response to either a specific tumor or a variety of cancers.

Applicant argues that based on a single publication on MAGE proteins, Kirkin et al, the Examiner asserts that the claimed PAGE4 polypeptide cannot be of use. Applicant argues that however many references support the idea that MAGE proteins have a specific and credible use, such as US 5,554,724, US 6,051,237, and US 6,392,016.

Applicant argues that it is not the intention of Applicant to argue that PAGE has exactly the same function or structure as MAGE, and that if one takes into consideration the MAGE information, one would believe that the disclosed utility is both specific and credible.

The arguments are not found to be persuasive.

Concerning the cited US patents, it is noted that each case is decided on its own facts. It is well settled that whether similar claims have been allowed to others is immaterial. See In re Giolito, 530 F.2d 397, 188 USPQ 645 (CCPA 1976) and Ex parte Balzarini 21 USPQ2d 1892, 1897 (BPAI 1991).

Further, although some cancer antigens could be used for treating cancer, which cancer antigen could be used for treating cancer is not predictable, in view of the overwhelming indication from the teaching in the art that cancer treatment is unpredictable (White et al, Smith et al, Boon et al, Ezzell et al, Spitler et al, and Kirkin et al, all of record).

Further, it is noted that Applicant misreprents the Examiner's position, when reciting that based on the teaching of a single reference on MAGE protein, Kirkin et al, the claimed PAGE4 polypeptide cannot be of use. It is noted that Kirkin et al teach not only the problem with MAGE family proteins, but also review a large number of melanoma associated antigens recognized by CTLs, including the group of cancer/testis antigens MAGE, BAGE, GAGE, PRAME and NY-ESO-01, wherein some of said antigens such as MAGE and GAGE have some structural similarity with the claimed PAGE-4 polypeptide, as asserted by Applicant. Based on the teaching of Kirkin et al, it is clear that there is an extreme limited number of peptide, that could induce CTLs, and also have in vivo anti-tumor activity (i.e. only one identified so far from MAGE proteins) among the reviewed numerous peptides from different categories of proteins. The Examiner position has been that: 1) in view of the overwhelming indication from the teaching in the art, i.e. White et al, Smith et al, Boon et al, Ezzell et al, Spitler et al, and Kirkin et al, all of record, and not just Kirkin et al alone, that cancer treatment is unpredictable, one cannot determine that SEQ ID NO:1 or its fragment could be used for treating cancer, and that further experimentation is required to determine what use is for the claimed polypeptide SEQ ID NO:1, or its fragments, and 2) because of this, the claimed polypeptide SEQ ID NO:1 and its fragments lack specific and substantial utility.

(5) The Declaration by Dr. Pastan

In addition, Applicant submits a Declaration by Dr. Pastan, stating that a nine amino acids polypeptide of SEQ ID NO:1 can be used to activate CTLs, that lyse prostate cancer cells *in vitro*.

The submission of the Declaration by Dr. Pastan is acknowledged and entered.

The Examiner takes note that the finding in the Declaration of Dr. Pastan is **post-filing**, thus reinforcing the assertion by the Examiner that at the time the invention was made, the specific and substantial utility of the claimed polypeptide SEQ ID NO:1 or its fragment could not be determined, and further experimentation is required to determine what use is for the claimed polypeptide or its fragments.

Moreover, it is noted that **the *in vitro* lysis of a prostate cancer cell line by a 9 amino acid fragment of SEQ ID NO:1 cannot be used to predict successful use of said fragment for treating cancer**, because one cannot predict that primary prostate cancer cells would overexpress SEQ ID NO:1, in a sufficient quantity to be recognized and lysed by CTLs as compared to prostate cancer cell line, in view of cell culture artifact, as taught by Drexler et al, Embleton et al, Hsu et al, Van Dyke et al, and Kunkel et al (see below), and view of the teaching of White et al, of record, that that antigen internalization or downregulation can cause repeat dosing to be unsuccessful due to the disappearance of the antibody target (p.126, paragraph before last), and further in view of the unpredictability of cancer treatment, as taught by Smith et al, Boon et al, Ezzell et al, and Spitler, Kirkin et al, all of record.

It is well known in the art that characteristics of cultured cell lines generally differ significantly from the characteristics of a primary tumor. Drexler et al (Leukemia and Lymphoma, 1993, 9:1-25) specifically teach, in the study of Hodgkin and Reed-Sternberg cancer cells in culture, that the acquisition or loss of certain properties during adaptation to culture systems cannot be excluded and that only a few cell lines containing cells that resemble the *in-vivo* cancer cells have been established and even for the *bona fide* cancer cell lines it is difficult to prove that the immortalized cells originated from a specific cancer cell (see attached abstract).

Further, Embleton et al (Immunol Ser, 1984, 23:181-207) specifically teaches that in procedures for the diagnosis of osteogenic sarcoma, caution must be used when interpreting results obtained with monoclonal antibodies that had been raised to cultured cell lines and specifically teach that cultured tumor cells may not be antigenically typical of the tumor cell population from which they were derived and it is well established that new artifactural antigens can occur as a result of culture (see attached abstract). Hsu (in Tissue Culture Methods and Applications, Kruse and Patterson, Eds, 1973, Academic Press, NY, see abstract, p.764) specifically teaches that it is well known that cell cultures *in vitro* frequently change their chromosomal constitutions (see abstract). Similarly, Van Dyke D L et al, 2003, Cancer Genetics and Cytogenetics 241: 137-141, teach that random loss of chromosome 21 (monosomy 21) in patients with hematologic diseases is rare and should be confirmed by in situ hybridization (FISH), and that in most diagnosed cases the random loss of chromosome 21 is more likely due to artifact of culture of cells obtained from the patients (abstract, and p. 140, first column, last two paragraphs before acknowledgments). Kunkel, P, et al, 2001, Neuro-oncology 3(2): 82-88, teach that teach that scatter factor/hepatocyte growth factor is overexpressed in most tumors examined, including glioblastomas, and that the lack of expression of scatter factor/hepatocyte growth factor in most cultured glioblastoma cells is not representative of the in vivo situation, and most likely represents a culture artifact (abstract). The evidence presented thus clearly demonstrates that in cell culture systems, in general, and in cancer derived cell lines in particular, that artifactural chromosome constitutions and antigen expression are expected and must be taken into account when interpreting data received from cell line assays.

Moreover, even if SEQ ID NO:1 or its fragment could induce CTLs that lyse primary cancer cells in vitro, further experimentation is required to determine whether SEQ ID No:1 or its fragment could be used for treating patients having cancers expressing SEQ ID NO:1, because of the following reasons:

a) Even if activated CTLs are significantly increased, the therapeutic success remains unpredictable due to inconsistencies in antigen expression or presentation by tumor cells, as taught by Boon et al, of record (p.178, paragraph before last paragraph).

b) Further, antigen overload, due to antigen shedding by actively growing tumor, could block specifically either cytotoxic or proliferative responses of tumor specific T cells, as taught by Smith et al, of record (p. 847, last paragraph bridging p.848 and p.848).

c) Many tumors progressively lose MHC representation at the surface of the cell, and the loss of surface Class I MHC could severely limits the possibilities for cytotoxic T cells specific for a tumor specific antigen to find said tumor specfic antigen in the necessary MHC context , as taught by Smith et al, of record (p.484).

d) This unpredictability of cancer treatment is further confirmed by the teaching of Kirkin et al, of record, i.e., among several peptides of MAGE protein family that could be recognized by CTL in vitro, so far only one peptide of MAGE-3 has been shown to have limited anti-cancer activity (Kirkin et al, p.666), and the teaching of White et al, Smith et al, Boon et al, Ezzell et al, Spitler et al, and Kirkin et al, all of record, that cancer treatment is unpredictable.

Thus, the disclosure satisfies none of the three criteria of a specific, substantial, and credible utility. *See In re Kirk*, 153 USPO 48, 53 (CCPA 1967) (quoting the Board of Patent Appeals, 'We do not believe that it was the intention of the statutes to require the Patent Office, the courts,

or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.')

The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide or fragments thereof. Because the claimed invention is not supported by a specific asserted utility for the reasons set forth, credibility of any utility cannot be assessed.

Claim Rejections - 35 USC § 112 First Paragraph, Enablement

Claims 1-8, 14-15, 17-18, 53-57 remain rejected under 35 U.S.C. 112, first paragraph, for reasons already of record in paper of 09/13/05.

A. Specifically, since the claimed invention is not supported by specific, substantial utility or a well established utility for the reasons set forth in the rejection under 35 USC 101 above, one skilled in the art clearly would not know how to use the claimed invention .

Applicant argues as follows:

The breath of the claims.

Applicant argues that the scope of the claims are limited to a single amino acid sequence of 102 amino acids and a limited number of fragments of this single amino acid sequence that can bind to MHC. Applicant argues that the claims have been amended to limit to prostate and uterine cancer and thus render the rejection moot.

The arguments are not found to be persuasive.

Contrary to Applicant's arguments, the breadth of the claims is broad.

The claims are not limited to a single amino acid sequence of 102 amino acids, SEQ ID NO:1, and a limited number of fragments of this single amino acid sequence that can bind to MHC.

Due to the open language "a polypeptide comprising 8 to 11 contiguous amino acids of SEQ ID NO:1" of claim 1, the polypeptides of claims 1, 2, 7, 17 encompass unknown sequences attached to 8 to 11 contiguous amino acids of SEQ ID NO;1, wherein the effect of the attached unknown sequences on the function of the claimed polypeptide is unpredictable, in view of the teaching of Bowie, of record.

Further, it is noted that the claimed "immunogenic composition" of claims 2, 4, 7, 8 encompass peptides that not only could bind to MHC I molecule, but also could induce CTL response, in view of the disclosure of the specification that "an immunogenic composition" refers to a peptide of PAGE-4 protein, when bound to a MHC I molecule, induces a measurable CTL response against cells expressing PAGE-4 protein (p.8, lines 30-34). Moreover, the claims encompass a genus of specific peptides of SEQ ID NO:1 that binds to MHC class I with sufficient affinity to induce CTLs response and lysis of primary cancer cells by said CTLs.

In addition, the claims are not limited to the composition claims. Claims 14-15, 17-18 are drawn to a method for inhibiting growth of any malignant cell expressing SEQ ID No:1, using SEQ ID NO:1 or its fragment, in view that the claims have been not been amended to limit to prostate and uterine cancer.

The breath of the claims is broad, in view of the following reasons: 1) the specification only discloses the structure of the polypeptide SEQ ID NO:1, 2) the specification does not have any objective evidence showing that SEQ ID NO:1 is expressed or overexpressed in cancer patients, and that SEQ ID NO:1 or a fragment thereof could be successfully used for treating cancer, and 3) the specification does not disclose which peptide of SEQ ID NO:1 could bind to MHC with properties that are necessary for the utility of the claimed peptides, i.e. with sufficient affinity, and having the ability to induce CTLs response and lysis of primary cancer cells.

The nature of the invention.

Applicant argues that the nature of the invention is limited to specific amino acid sequences and that methods for synthesizing the sequences are routine and/or automated.

The arguments are not found to be persuasive.

The nature of the invention is complex. The invention is not limited to specific amino acid sequences. The polypeptides of claims 1, 2, 7, 17 encompass unknown sequences attached to 8 to 11 contiguous amino acids of SEQ ID NO;1, wherein the effect of the attached unknown sequences on the function of the claimed polypeptide is unpredictable, in view of the teaching of Bowie, of record,supra. Moreover, the claims encompass a genus of specific peptides of SEQ ID NO:1 that binds to MHC class I with sufficient affinity to induce CTLs response and lysis of primary cancer cells by said CTLs. In addition, the claims are not limited to the composition claims. Claims 14-15, 17-18 are drawn to a method for inhibiting growth of a malignant cell expressing SEQ ID No:1, using SEQ ID NO:1 or its fragment.

Further, although methods for synthesizing the sequences are routine and/or automated, which 8 to 11 contiguous amino acids of SEQ ID NO;1 binds to MHC class I with sufficient

affinity, and is useful for diagnosis or treatment of cancer is not disclosed and cannot be predicted, in view of the teaching in the art, supra.

The state of the prior art.

Applicant argues that computer program exists that will predict which nine consecutive amino acids will bind to MHC.

The arguments are not found to be persuasive.

Although computer program exists that will predict which nine consecutive amino acids will bind to MHC, however, which 8 to 11 contiguous amino acids of SEQ ID NO;1 binds to MHC class I with sufficient affinity, and is useful for diagnosis or treatment of cancer is not disclosed and cannot be predicted, in view of the teaching in the art, supra.

The level of skill of one of ordinary skill in the art.

Applicant argues that the level of skill of the average molecular biologist or immunologist is high.

The Examiner takes note that although the level of skill in the field of molecular pathology is high, however, it would be undue experimentation for one of skill in the art to practice the claimed invention, due to the high level of unpredictability of the art (see below).

The level of predictability in the art.

Applicant argues that computer program can be used to predict which eight to ten consecutive amino acids of a specified polypeptide are likely to bind to MHC, and to rank polypeptides in order of predicted strength of the binding. Applicant argues that once the polypeptides are identified, a biological assay can be used to confirm that the eight to ten consecutive amino acids actually bind MHC.

The arguments are not found to be persuasive.

The level of unpredictability is high. One cannot predict that the claimed polypeptide is overexpressed on the surface of primary cancer cells with sufficient quantity such that it can be recognized and lysed by specific CTLs, when based on the disclosure in the instant specification that the polynucleotide encoding SEQ ID NO:1 is underexpressed in prostate cancer (figure 4), and is overexpressed in uterine cancer (figure 2B) as compared to corresponding normal control, and in view of the unpredictability of protein level, when based solely on the level of the encoding polynucleotide, as taught by Brennan et al, Zimmer et al, Eriksson et al, Hell et al, and Guo et al, Fu et al, Yokota et al, supra. Further, although computer program can be used to predict which eight to ten consecutive amino acids of a specified polypeptide are likely to bind to MHC, binding to MHC by itself is not sufficient to predict which peptides are useful for diagnosis or treatment of cancer, because not any peptide that bind to MHC could induce CTLs response, and lysis of primary cancer cells by said CTLs, in view of the teaching of teaching in the art, supra. Further, one cannot predict that SEQ ID NO:1 or fragments thereof can be used for treating cancer, in view that cancer treatment is highly unpredictable, as taught in the art, supra.

The amount of direction provided by the application.

Applicant argues that the specification discloses SEQ ID NO:1, peptides of 8-10 amino acids of SEQ ID NO:1, that have binding motifs for HLA-A2 with specific anchoring residues in second and positively charged amino acid at the position nine. Applicant argues that the specification discloses the methods and computer based programs for predicting MHC binding motifs.

The arguments are not found to be persuasive.

There is insufficient guidance from the specification. The specification does not disclose that the polypeptide SEQ ID NO:1 is overexpressed in primary cancer cells as compared to normal corresponding control cells, nor any objective evidence showing that SEQ ID NO:1 or its fragments could be used for diagnosing or treating cancer. Further, the specification does not describe which peptide fragment of SEQ ID NO:1 could binds to MHC class I with sufficient affinity, and could induce CTLs response and lysis of primary cancer cells by said CTLs, such that the claimed peptide could be used for diagnosis or treatment of cancer.

Further, the disclosed peptides of 9 or 10 amino acids in length, with anchoring amino acids at position 2 and 9 that bind to MHC class I, are drawn to a genus of peptides that bind to MHC class I with any affinity, and is not a sufficient description for the encompassed specific subgenus of the MHC class I binding-peptide fragments of SEQ ID NO:1, that could induce CTLs response and lysis of primary cancer cells by said CTLs, because besides the anchoring amino acids at positions 2 and 9, amino acids at positions 1, 3-8, or 10 of an 8-10 amino acids peptide also influence its binding affinity to MHC class I, wherein a sufficient affinity binding is critical for inducing CTL response and lysis of primary cancer cells by said CTLs, in view of the teaching of WO 94/020127 A1, and Visseren et al, supra.

The existence of working examples.

Applicant argues that SEQ ID NO:1 is provided, as are examples of isolating the nucleic acid encoding SEQ ID NO:1, and expression vectors encoding SEQ ID NO:1.

Applicant argues that a fragment of PAGE-4 can be used for producing antibodies.

The Examiner takes note that although the specification discloses the full length polypeptide SEQ ID NO:1 and a fragment of SEQ ID NO:1, that can produce antibody to SEQ

ID NO:1, there is no example or objective evidence showing the expression level of SEQ ID NO:1 in primary cancer cells as compared to normal control, which objective evidence is necessary for one to determine whether SEQ ID NO:1 could be used for diagnosis of cancer, in view of the unpredictability of the level of protein, when based solely on the level of the encoding mRNA, as taught by the art, supra.

Further, there is no example of structure of the peptides that could bind to MHC with sufficient affinity, and could be used to induce CTLs response, and lysis of primary cancer cells by said CTLs, nor any data or objective evidence showing that SEQ ID NO:1 or its fragment could be used for treating cancer.

It is noted that MPEP 2164.03 teaches that "the amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability of the art. In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The amount of guidance or direction refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature ot the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to explicitly stated in the specification. In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as how to make and use the invention in order to be enabling."

The quantity of experimentation needed to make or use the invention.

Applicant argues that very limited routine experimentation is required to produce the polypeptide SEQ ID NO:1. Applicant argues that that a computer program publicly available

could be used to identify epitopes that bind MHC, which are then synthesized. Applicant argues that once synthesized, the polypeptides must be screened for its binding to MHC and induction of CTL response, using the methods provided in the specification.

The arguments are not found to be persuasive.

The quantity of experiment to determine whether SEQ ID NO:1, or a fragment thereof, could be successfully used for diagnosis or treating cancer is extremely large. It would be undue experimentation for one of skill in the art to screen for the claimed peptides, that would bind to MHC class I with sufficient affinity, and could be used to elicit CTLs response, wherein said CTLs could kill primary cancer cells, in view of 1) the unpredictability of sufficient level of the polypeptide SEQ ID NO:1 in primary cancer tissue as compared to normal control tissue, 2) the unpredictability of which 8-10 amino acids peptides from SEQ ID NO:1 would bind to MHC class I with sufficient affinity, and could be used to elicit CTLs response, wherein said CTLs could kill primary cancer cells, and 3) the unpredictability of successful use of SEQ ID NO:1 or a fragment thereof for cancer treatment, and further in view that screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays, and by inference suggestions of structural analysis, are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention.

In summary, given 1) the unpredictability of sufficient level of the polypeptide SEQ ID NO:1 in primary cancer tissue as compared to normal control tissue, 2) the unpredictability of which 8-10 amino acids peptides from SEQ ID NO:1 would bind to MHC class I with sufficient affinity, and could be used to elicit CTLs response, wherein said CTLs could kill primary cancer

cells, and 3) the unpredictability of the successful use of SEQ ID NO:1 for cancer treatment, and in view of the complex nature of the invention, and further in view of insufficient disclosure in the instant specification, and little is known in the art concerning the claimed invention, it would be undue experimentation for one of skill in the art to practice the claimed invention.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, JEFFREY SIEW can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MINH TAM DAVIS

April 29, 2006

JEFFREY SIEW
SUPERVISORY PATENT EXAMINER